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Mixed connective tissue disease

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A B S T R A C T

The concept of mixed connective tissue disease (MCTD) as a separate connective tissue disease (CTD) has persisted for more than four decades. High titers of antibodies targeting the U1 small nuclear ribonucleoprotein particle (U1 snRNP) in peripheral blood are a sine qua non for the diagnosis of MCTD, in addition to distinct clinical features including Raynaud's phenomenon (RP), "puffy hands," arthritis, myositis, pleuritis, pericarditis, interstitial lung disease (ILD), and pulmonary hypertension (PH). Recently, population-based epidemiology data from Norway estimated the point prevalence of adult-onset MCTD to be 3.8 per 100,000 and the mean annual incidence to be 2.1 per million per year, supporting the notion that MCTD is the least common CTD. Little is known about the etiology of MCTD, but recent genetic studies have confirmed that MCTD is a strongly HLA (human leukocyte antigen)-linked disease, as the HLA profiles of MCTD differ distinctly from the corresponding profiles of ethnically matched healthy controls and other CTDs.

In the first section of this review, we provide an update on the clinical, immunological, and genetic features of MCTD and discuss the relationship between MCTD and the other CTDs. Then we proceed to discuss the recent advances in therapy and our current understanding of prognosis and prognostic factors, especially those that are associated with the more serious pulmonary and cardiovascular complications of the disease. In the final section, we discuss some of the key, unresolved questions related to anti-RNP-

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associated diseases and indicate how these questions may be approached in future studies.

Introduction

The concept of mixed connective tissue disease (MCTD) as a separate immune-mediated connective tissue disease (CTD) was first introduced by Gordon C. Sharp and coworkers > 40 years ago, but there is still no consensus regarding the disease definitions, the classification criteria, or the relationship with other CTDs [1]. Some rheumatologists argue that MCTD is a distinct disease entity; others believe that it represents an overlap syndrome or an early and unspecific phase of an evolving, more distinct CTD; however, few studies still disregard the whole concept [2–4].

In their initial report, Sharp and coworkers described MCTD as a mild disease with favorable outcomes and an excellent response to oral prednisolone [1]. This description holds true for some patients, but the overall impression from published cohorts and case series is that MCTD is a complex disease, with large interindividual variations in clinical features, responses to therapy, and outcomes [5–12]. The disease appears in all age groups, but the peak incidence of MCTD is around 40 years [13]. Previous studies have reported that 7–23% of the total MCTD population have a juvenile onset [10,14]. Whether there are any systematic differences between adult and juvenile MCTD (JMCTD) remains unclear.

To date, there are no uniform guidelines for evaluating patients presenting with systemic disease features and a high titer of serum autoantibodies directed against the U1 ribonucleoprotein (anti-RNP), and there is no international consensus on how, when, and in whom MCTD should be diagnosed [8,9,15]. Nevertheless, most physicians working in the CTD clinics would probably agree that the diagnosis of MCTD should be considered in an anti-RNP-positive patient presenting with Raynaud's phenomenon [1,10,16,17], diffuse hand edema (“puffy hands”), and at least two of the following features: arthritis, myositis, leukopenia, esophageal dysmotility, pleuritis, pericarditis, interstitial lung disease (ILD) [18–24], or pulmonary hypertension (PH) [5,7–9,25,26]. However, none of these features are unique to MCTD. They can also be observed in patients with systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM), the three CTDs that mostly resemble MCTD. Diagnosing MCTD in clinical practice is therefore an issue of pattern recognition and clinical decision with rich possibilities for different opinions and practices across the rheumatology communities.

The four coexisting criteria sets for MCTD further complicate this issue (Supplementary Table 1). Even though all these four criteria sets were originally presented as diagnostic criteria, they are distinctly different (Table 1), and within a clinical MCTD population, they do not capture the same patients (Fig. 1). Three of the proposed criteria sets [27–29] were first presented at an international conference on MCTD held in Japan in 1986 and the last criteria set was published in France in 1991 [30]. Only two of these four criteria sets have been regularly used for research purposes in adult populations: the Alarcón-Segovia criteria and the Kasukawa criteria [28,29]. The Kasukawa criteria have mostly been used in juvenile MCTD (JMTCD) [12,28,29]. Sharp's modified criteria set has not been widely used for several reasons, the most obvious being their complexity and the need for autoantibody data that are no longer available from routine immunology laboratories (see Table 1). The limited use of the Kahn criteria may be related to accessibility as the criteria were originally presented in French, and the fact that they closely resembled one of the already published criteria sets (Table 1).

Compared to the other CTDs, the research activity on MCTD has been relatively low from the late 1990s. Unfortunately, as a result, a large proportion of the standard textbook references on MCTD include >20 years old and originate from relatively small and potentially skewed single-center hospital cohorts [5–12]. An extensive study of MCTD has not been conducted recently due to the following four interrelated reasons: (1) the controversies regarding the concept may have dampened the enthusiasm of some researchers; (2) the apparent rarity of the disease, with a concomitant lack of population-based epidemiology estimates, has made it difficult to plan and design MCTD studies; (3) the lack of